Biologics Primer: The Care of the patient on immunomodulators

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Disclosures

• None related to this talk
Objectives

- **Drug Features** - What is biologic therapy
- **Disease Features and efficacy** - treatment with biologics in various diseases and goals of therapy
- **Patient features** - patient demographics and co-morbidities may impact clinical decision making
- **General Preventive Care** - Health care maintenance
- **Reactivation of dormant pathogens** - Understanding risk of Tuberculosis, Hepatitis B, CMV
- **Cessation of therapy for procedures** - Non-invasive vs. invasive
- **Cancer and Biologics** - New agents with promises and challenges
- **Immune Complications** - Drug induced lupus, psoriasis and immunotherapy related colitis
Biologic Therapies- 2017

Monoclonal antibodies

• Anti-TNF
• Anti IL-12/23
• Anti-Integrin molecules
• Biosimilars on the horizon
Rationale to target TNF in inflammation

- **macrophage**
  - Increase in pro-inflammatory cytokines
  - Increase in chemokines

- **endothelium**
  - Increased adhesion molecules

- **Fibroblast**
  - Increase in acute phase reactants
  - Increase in metallo-proteases
  - Increase collagen synthesis

- **Epithelial cell**
  - Increase in ion transport
  - Increase permeability

INFLAMMATION
CELL INFILTRATION
TISSUE INJURY
MUCOSAL COMPROMISE
Biologics that neutralize TNF-α

- **Chimeric monoclonal antibody**: Infliximab, Adalimumab, Golimumab
- **Human monoclonal antibody**: Certolizumab pegol
- **Human recombinant receptor/Fc fusion protein**: Infliximab, Adalimumab, Golimumab, Etanercept

**Humanized Fc-Free Fab’ fragment**

FDA approved for Crohn’s disease, ulcerative colitis, rheumatoid arthritis, psoriatic arthritis and plaque psoriasis
Efficacy of Biologic Therapy

- Varies significantly across indications: high in psoriasis and good in arthritis and Inflammatory bowel disease
- Not curative therapy and therefore maintenance is required for all indications
- Due to high cost, FDA approval is based on significant improvement over conventional therapy
- Goals of therapy:
  - Induce and maintain symptom-free remission
  - Prevent disease complications
  - Improve quality of life
Route of Delivery

**Infusion therapy**
- Administered at infusion centers
- Requires monitoring
- Cost:
  - Loss of work time
  - Medication cost
  - Facility cost

**Self injections**
- Prefilled syringes
- Compliance
- Convenience
Risks with Biologic Therapies

- Infusion / Injection site reactions / Immunogenicity
- Infections
- Autoimmunity
- Malignancies
- Other
  - Cardiac
  - Hepatic
Making sense of safety data

• Relative vs. absolute risks
  – Relative risks in most studies are high
  – Absolute risks are high
  – Risk of Lymphoma:
    • 2:10,000 → 6:10,000

• Concomitant risk factors:
  – Age
  – Sex (e.g. Hepatosplenic T cell lymphoma)
Case 1

- 27 year old female has been on infliximab for Crohn’s Disease. She stopped treatment during pregnancy. Her symptoms returned 2 weeks after she stopped breastfeeding. She restarted infusions and developed severe chest tightness, shortness of breath, and hypotension while receiving the infusion.
Infusion Reactions

Infusion Reaction

Acute reaction (within 24 hours)
- IgE-mediated Type I hypersensitivity
- Other Antibody to biologic

Delayed reaction (>48 hours)
- Serum sickness-like
  - Antibody to biologic
  - Type III hypersensitivity?
- Other
  - Lupus-like reaction
  - Viral syndrome
  - IBD flare
  - Nonspecific

Clinical Complications Associated with Antibodies to Infliximab (ATI)

- Attenuated response
- Acute and delayed infusion reactions
- Lower postinfusion infliximab serum levels
- Serum sickness-like reactions

ATI = antibody to infliximab
Patient reports hives after taking the third dose of adalimumab, she emails you a picture of rash around the injection site. What is the most appropriate course of action?

A. Stop the medication immediately
B. Ask her to pre-medicate with an over the counter antihistamine
C. Pick a different injection site spot
Factors that prevent antibody formation

- Higher initial dose (10mg/kg < 5mg/kg < 3mg/kg < 1mg/kg)
- Scheduled dosing << Episodic dosing
- Combination therapy with AZA/6MP/MTX < Mono therapy
- Premedication with IV Hydrocortisone < no premedication
- Design of construct - human < humanized < chimeric antibody

Antibody to IFX or ADA can lead to loss of response and significant side effects.
Case 2

- 33 year old IT executive calls his gastroenterologist to report few weeks of productive cough, night sweats, and fever. He has history of ulcerative colitis, well-controlled on infliximab for the past year. GI nurse asks patient to call PCP. Patient reports sick contacts and has not travelled. He is a native of India and moved to USA 6 years ago.

- Diagnosis? Influenza or pneumonia?
Infection in the TREAT Registry Patients on biologics in IBD: Multivariable Logistic Regression Analysis

- Serious infection
  - Prednisone: RR=2.33; (95% CI=1.50-3.62; \( P<.001 \))
  - Narcotics: RR=2.41; (95% CI=1.54-3.76; \( P<.001 \))
  - Moderate or severe CD: RR=2.13; (95% CI=1.06-4.26; \( P=.03 \))
  - Infliximab *not* predictive: RR=0.93; (95% CI=0.59-1.49)

### Serious Infections in IBD

<table>
<thead>
<tr>
<th></th>
<th>Within 3 mos. of infusion</th>
<th>Not within 3 mos. of infusion</th>
<th>Relative Risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious Infection</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Per 100 pt-yrs</td>
<td>1.19</td>
<td>0.67</td>
<td>1.77</td>
<td>1.27-2.46*</td>
</tr>
</tbody>
</table>

*p<0.001*
Case 2

- Patient went to MGH ER, he appeared ill and had low grade temperature. Chest X ray showed diffuse infiltrates and was admitted for IV antibiotics. On day 3, microbiology lab pages on call doctor with a positive result on sputum examination.

- Diagnosis?

- Could this have been prevented?
Tuberculosis

- Immune suppression dose intensity/mechanism influences risk
- Rate of TB in patients treated with biologics continues to decrease. *Prescreen and treat TB before biologic is given for inflammatory disease*
- TSPOT / Interferon gamma based assay is considered superior to PPD and should be performed yearly
- Physician education programs have led to decreased rates and mortality- *recognize symptoms*
- Continued vigilance needed throughout the course of treatment
Case 2 Question

Which of the following is least likely to reactivate on long term biologic activity?

A. Hepatitis B  
B. Tuberculosis  
C. Hepatitis C  
D. CMV
Infections on biologics

- Infections
  - Pneumonia
  - Line sepsis
  - Urinary tract infection
  - Intra abdominal abscess

- Re-activation of dormant pathogens
  - Tuberculosis
  - Hepatitis B
  - Coccidiomycosis
  - Histoplasmosis
  - CMV- CMV colitis
  - Zoster
Case 3

31 year old female is your office for an annual physical, and she mentions that she is on a biologic therapy for an immune-mediated condition. What are some of the areas you should focus the assessment?

A. General Wellness screen including exposures at work, home and travel.
C. Skin examination
D. Immunizations screen
E. Review of systemic steroids and Bone health
F. Cancer screens, breast exam, PAP smears
G. Labs with focus on vitamin D, B12, and iron studies
Immunizations

**Figure:** Bar chart showing the percentage of patients in different groups:

- **IBD TNF/IM:** 45%
- **IBD ASA:** 80%
- **CTRL:** 84%

**Statistical Significance:**
- IBD TNF/IM vs. CTRL: P=0.07
- IBD ASA vs. CTRL: P=0.01

References:
### Inactivated Vaccines

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Check Titer</th>
<th>If already on IMM / BIOLOGIC</th>
<th>Family members</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV (for females 9-26 years)</td>
<td>No</td>
<td>3 doses (0,2,6)</td>
<td>Yes</td>
</tr>
<tr>
<td>Influenza</td>
<td>No</td>
<td>Annual. Avoid live attenuated (Flumist)</td>
<td>Administer inactivated. Avoid live attenuated</td>
</tr>
<tr>
<td>Pneumococcal</td>
<td>No</td>
<td>Yes. Repeat in 5 years x 1</td>
<td>Yes</td>
</tr>
<tr>
<td>Meningococcal</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Yes</td>
<td>3 doses. Check titers at 1 month after last dose</td>
<td>Yes</td>
</tr>
</tbody>
</table>
## Live Vaccines

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Check Titer</th>
<th>If already on IMM / BIOLOGIC</th>
<th>Family members</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMR</td>
<td>Yes</td>
<td>Contraindicated</td>
<td>Yes</td>
</tr>
<tr>
<td>Zoster (for age &gt; 60)</td>
<td>No</td>
<td>Contraindicated*</td>
<td>Yes (except if vaccine related rash)</td>
</tr>
<tr>
<td>Varicella</td>
<td>Yes</td>
<td>Contraindicated</td>
<td>Yes (except if vaccine related rash)</td>
</tr>
</tbody>
</table>

* Can consider if short term steroids or low-dose immune suppression

Live vaccines are contraindicated if plans to start biologic therapy in 1-3 months

## Health maintenance in IBD

### The “Checklist”

<table>
<thead>
<tr>
<th>Year</th>
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<tbody>
<tr>
<td>PPD</td>
</tr>
<tr>
<td>Vaccinations</td>
</tr>
<tr>
<td>• Hepatitis A</td>
</tr>
<tr>
<td>• Hepatitis B</td>
</tr>
<tr>
<td>• HPV</td>
</tr>
<tr>
<td>• Influenza</td>
</tr>
<tr>
<td>• Pneumococcal</td>
</tr>
<tr>
<td>• Td/Tdap</td>
</tr>
<tr>
<td>• MMR*</td>
</tr>
<tr>
<td>• Varicella*/Zoster*</td>
</tr>
<tr>
<td>Annual exams</td>
</tr>
<tr>
<td>• Pap smear</td>
</tr>
<tr>
<td>• Breast/prostate</td>
</tr>
<tr>
<td>• Blood pressure</td>
</tr>
<tr>
<td>• Ophthalmologic</td>
</tr>
<tr>
<td>• Skin cancer</td>
</tr>
</tbody>
</table>

MoscLaura M. Inflamm Bowel Dis 2009 Sep;15(9):1399-409.
Health maintenance in IBD

The “Checklist”

<table>
<thead>
<tr>
<th>Radiology</th>
<th></th>
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<tbody>
<tr>
<td>• DXA scan</td>
<td></td>
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<tr>
<td>• Mammogram</td>
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<table>
<thead>
<tr>
<th>Colonoscopy</th>
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</thead>
<tbody>
<tr>
<td>• Postoperative</td>
<td></td>
<td></td>
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<tr>
<td>• Dysplasia surveillance</td>
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<table>
<thead>
<tr>
<th>Laboratory exam</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>• CBC</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>• LFT’S</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Creatinine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• B12/folate/iron</td>
<td></td>
<td></td>
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<tr>
<td>• 25 OH vitamin D</td>
<td></td>
<td></td>
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<tr>
<td>• Lipids/glucose</td>
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<table>
<thead>
<tr>
<th>Other</th>
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</thead>
</table>
Question 3

Which of the following vaccines are contraindicated in patients with IBD on anti-TNF therapy?

A. Hepatitis B  
B. Pneumococcal  
C. Zoster (Shingles)  
D. HPV
Question 4

Which of the following skin lesions are increased in patients on immune suppression?

A. Melanoma
B. Non melanoma skin cancer
C. A and B

Long et al *Gastroenterology*. 2012
# Malignancy Risk in Immunosuppressed Patient

<table>
<thead>
<tr>
<th>AZA/6MP</th>
<th>Anti TNF</th>
<th>Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non Hodgkin Lymphoma</td>
<td>Melanoma</td>
<td>Hepatosplenic T cell Lymphoma</td>
</tr>
<tr>
<td>Acute Myeloid Leukemia</td>
<td>Non-Hodgkin Lymphoma</td>
<td>Non-Hodgkin Lymphoma</td>
</tr>
<tr>
<td>Myelodysplasia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatosplenic T cell Lymphoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Melanoma Skin Cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary Tract Cancer</td>
<td></td>
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</tr>
</tbody>
</table>

Hepatosplenic T cell lymphoma affects only adolescent males.
56 year old male on biologic therapy is undergoing a knee replacement. He wants to know what he should do with his next biologic dose?

A. Continue treatment
B. Hold treatment
Hold biologics if procedure is invasive

Hold

Treat

Invasive surgery

Pap smear

Skin Biopsy

Colonoscopy
Personalizing therapy- patient co-morbidity

- Top down
- Pediatrics
- Pregnancy
- Elderly
- Concurrent IM use
- Post-op
- 2nd and 3rd anti TNF
- Cancer
- Biologic Users
Case 6

81 year old male with ulcerative colitis is not responding to conventional therapy. GI doctor has kept him on steroids for > 12 months.

Is there a risk to treat with biologic?
IBD in Elderly

- Incidence of IBD is increasing worldwide
- 2nd peak incidence in 7th decade
- 6th & 7th decade
- Chronic relapsing-remitting nature
- Unaltered life expectancy

Aging of the general population

Higher number of elderly IBD patients

Cosnes, Gastroenterology May 2011
Picco, Gastroenterology Clin, 2009
Durability of Biologic Therapy

Increased risk of Infection is older patients

Case 7

45 year old female has history of Crohn’s disease and 3 years ago was treated for breast cancer. She was on a biologic for 5 years but stopped because of diagnosis of breast cancer. She did not restart biologic after cancer treatment was complete but is now flaring.

Is there a risk to treat this patient with biologic? Can patients with personal history of cancer be treated with biologics?
Biologics and Cancer

• Patients with IBD are at an increased risk of developing intestinal malignancy
  – Risk estimated at 6% at 20 years

• IBD treatment regimens may also compound the risk of malignancy
  – Estimated 2-5 fold increase in risk of lymphoma (Non-Hodgkin’s)
Biologics and Cancer

• Safety of immunosuppressive treatment in treatment of IBD in patients with an established history of cancer is unclear

• Effect of chemotherapeutic regimen on influencing natural history of underlying IBD is also unknown
Patients with personal history of cancer can take biologics but require close monitoring.

Decision regarding initiating of biologic therapy should be made in close consultation with oncologist.

We need large registries to define the frequency of recurrent cancer on biologics.
Case 8

45 year old female has Crohn’s disease and is on an anti-TNF for 5 years. At her routine physical she reports to PCP that she is very fatigued. She gets a rash when exposed to the sun. She has significant stiffness in the morning.

What is this entity? Can this be autoimmunity?
Autoimmunity in Clinical Trials – Newly ANA/anti-dsDNA Positive

• CD Studies* (All ACCENT I and II patients received infliximab)
  
<table>
<thead>
<tr>
<th>Test</th>
<th>Placebo</th>
<th>Infliximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA</td>
<td>0%</td>
<td>40%</td>
</tr>
<tr>
<td>anti-dsDNA</td>
<td>0%</td>
<td>20%</td>
</tr>
</tbody>
</table>

• RA Studies

<table>
<thead>
<tr>
<th>Test</th>
<th>Placebo</th>
<th>Infliximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA</td>
<td>18%</td>
<td>58%</td>
</tr>
<tr>
<td>anti-dsDNA</td>
<td>0.3%</td>
<td>18%</td>
</tr>
</tbody>
</table>

• Psoriasis Studies

<table>
<thead>
<tr>
<th>Test</th>
<th>Placebo</th>
<th>Infliximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA</td>
<td>6%</td>
<td>58%</td>
</tr>
<tr>
<td>anti-dsDNA</td>
<td>0.3%</td>
<td>20%</td>
</tr>
</tbody>
</table>

• All Studies*

<table>
<thead>
<tr>
<th>Test</th>
<th>Placebo</th>
<th>Infliximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA</td>
<td>12%</td>
<td>53%</td>
</tr>
<tr>
<td>anti-dsDNA</td>
<td>0.2%</td>
<td>18%</td>
</tr>
</tbody>
</table>

* Includes clinical trials with adult patients (REACH not included) & ACT 1 data for Wks 0-30 only
Drug induced lupus like syndrome

- 17 of 5,706 patients (0.29%) developed lupus-like symptoms while on study
  - 3 CD patients, 1 UC patient
  - 5 RA patients, 1 AS patient
  - 7 psoriasis patients

- Symptoms resolved with discontinuation and short-term steroid treatment

- Males = Females

- Incidence is likely higher than reported

- Diagnosis is based on clinical picture. Also check ANA, anti dsDNA and anti histone
Drug induced psoriasis

- New onset psoriasis has been reported in up to 2% of patients initiating anti-TNF therapy
- Majority of patients can stay on the biologic and treat psoriasis using topical steroids
- Some patients have to discontinue treatment
- Rates slightly higher in women
- Class effect likely will recur with switching to another anti-TNF
Leukocyte Trafficking as a Target in Inflammatory Bowel Disease

Vedolizumab

Rutgeerts P. Gastroenterology 2009;136:1182–1197
Gut selective Biologics may be safer

<table>
<thead>
<tr>
<th>Condition</th>
<th>Vedolizumab</th>
<th>Anti-TNF therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious Infection</td>
<td>-</td>
<td>+/-</td>
</tr>
<tr>
<td>Opportunistic</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Demyelinating</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Autoimmune (SLE, vasculitis)</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Dermatologic (psoriasis)</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Cardiac (CHF)</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Pulmonary (Sarcoidosis, ILD)</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

Caveat: most new drugs have additional toxicities identified during post-marketing surveillance

Kopylov U. GCNA 2014
Feuerstein JD. GCNA 2014
Summary

• Use of biologic therapy is in its second decade and is considered safe and highly effective

• Patients on these agents represent all age groups and therefore present a challenge to clinicians

• Clinical guidelines have been established for monitoring patients on these drugs